REMARKS

Claims 9 and 11 are pending in this application. Claim 9 has been amended to define a pharmaceutical composition consisting essentially of thalidomide as a single principle ingredient. The subject matter of claim 10 has been incorporated in claim 9. Claim 10 has been cancelled. Claim 11 has been amended to define the amount of thalidomide as 50 to 800 mg.

This application claims priority from corresponding ROC (Taiwan) Application No. 089101826 ("the ROC application"), filed on 2 February 2000. A certified copy of the ROC application was submitted to the USPTO and a copy of the postcard receipt, which shows that the USPTO acknowledged receipt of the certified copy is attached.

According to the Official Action claims 9 to 11 are rejected as being anticipated under 35 USC 102 by Am. Jour. Clin. Oncol. 23 (3): 319-321, 2000 ("Citation 1"), US 6,617,354 ("Citation 2") and US 6,231,536 ("Citation 3").

This rejection is respectfully traversed. As stated above, this application was filed with a priority claim to ROC application 089101826. The specification of the ROC application is substantially the same as that of the subject application as filed and does provide a written description and enabling disclosure for claims 9 and 11 of the subject application. An English translation of the ROC application is attached. The applicant is entitled to the priority date for the claimed invention. A copy of Am. Jour. Clin. Oncol. 23(3):319-321, 2000 downloaded from the website (http://www.amjclininicaloncology.com/pt/re/ajco/toc.00000421-200006000-00000.htm;jsessionid=BwXObkkmdI129DidLAGLfgHqHHynnBXfRuAnns2x7PwfkqEwOSbMy!113108930!-949856032!9001!-1) shows that Citation 1 was published in the June 2000 issue of American Journal of Clinical Oncology. Citation 1 was published in June 2000, which is later than the priority date of the present application and since this application is entitled to the priority date of the ROC application, the novelty rejection in view of Citation 1 should be withdrawn.

The present invention relates to use of thalidomide *per se* for treating hepatocellular carcinoma. Examples 2 and 3 illustrate a thalidomide treatment to patients having hepatocellular carcinoma, and show that oral administration of capsule(s) containing thalidomide as a single principle ingredient significantly reduced the tumor size and/or the serum level of alpha-fetoprotein in the patients. Citation 2 is intended to solve the stability problem of anti-angiogenesis *proteins/peptides*. The citation teaches that cis-unsaturated fatty acid (c-UFAs) can be used to stabilize and potentiate actions of anti-angiogenesis agents in the treatment of cell proliferative disorders, and provides a composition for the treatment of cancers wherein conventional anti-angiogenesis proteins/peptides are formulated together with c-UFAs. Citation 2 at best mentions a general concept of using anti-angiogenesis agents in the treatment of cell proliferative disorders (e.g., tumors) based on their inhibitory activity on the generation of new blood vessels so that supply of nutrients and energy via blood stream to tumor regions is blocked, and illustrates a number of conventional anti-angiogenesis agents to be used in combination with c-UFAs. However, the citation does not specifically indicate that thalidomide as a single principle ingredient is effective in treating the specific cancer, hepatocellular carcinoma, as taught and claimed in the present application.

Citation 3 is directed to a treatment method for cancers with ultrapheresis procedures to stimulate the patient's immune system to attack solid tumors. The tumor therapeutic effects shown in Example 4 of the citation already occurred because of the ultrapheresis procedures and should not be attributed to the administration of thalidomide. The anti-angiogenesis agents taught in Citation 3 are used as a combined therapy with the ultrapheresis procedures rather than a single administration. The citation does not disclose that a single administration of thalidomide is effective for treating hepatocellular carcinoma as taught in the present invention.

Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475,

31 USPQ 1671 (Fed. Cir. 1994). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Res. Found. v. Genentech, Inc.,* 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991).

Claim 9 now includes the conjunction phrase "consisting essentially of" and defines thalidomide as a single principle ingredient and an effective amount of the same contained in the pharmaceutical composition to be administered. This is not taught or disclosed in either of the cited references 2 and 3.

Therefore, since each and every element of the claimed invention is not disclosed in either of citations 2 and 3, and applicants are entitled to the priority date of their ROC application, it is respectfully requested that the rejection be withdrawn.

According to the Official Action claims 9 to 11 are rejected as being obvious under 35 USC 103 over US 5,629,327 ("Citation 4"), Masiero et al. ("Citation 5") and US 5,696,092 ("Citation 6").

This rejection is respectfully traversed.

Citation 4 is directed to a group of compounds (including thalidomide) having anti-angiogenesis activity. This citation shows that thalidomide can be used to treat corneal neovascularization and generally suggests some diseases involving undesired angiogenesis such as rheumatoid and hemangiomas treatable by thalidomide. There is no disclosure or suggestion that thalidomide can be used to treat cancer, specific types of cancer and certainly no disclosure or suggestion that thalidomide can be used to treat hepatocellular carcinoma.

Citation 5 discloses four anti-angiogenesis agents including thalidomide under investigation in the USA, wherein thalidomide is currently tested in phase II of clinical trials for prostate cancer, glioblastoma and breast cancer. However, this

citation does not suggest or imply other types of cancers treatable with thalidomide, especially hepatocellular carcinoma.

Citation 6 focuses on the use of compounds that inhibit arachidonic acid release by cells of a tumor for preventing metastasis of the tumor. It is not the teachings in Columns 8 to 9 of the citation as indicated by the examine that liver cancers are specifically treatable with anti-angiogenesis agents and such cancers respond in a similar fashion to such agents as compared to prostate cancer. Instead, Citation 6 lists a variety of cancers treatable with arachidonic acid release inhibitors as mentioned in the citation, and states that a prostate cancer is one example of the citation and other cancers that may be treated in analogous or identical fashion are within the scope of the disclosure of the citation. Citation 6 at best teaches that additional therapeutic agents such as angiogenesis inhibitors can be used *in combination with* the arachidonic acid release inhibitors, see Column 13, lines 22 to 23, but does not provide any hint with respect to the treatment of a specific type of cancer with an anti-angiogenesis agent itself, or mention the use of thalidomide itself for treating hepatocellular carcinoma as claimed in this application.

Citations 4 to 6 as well as Citations 1 to 3 provide no motivation or teachings with respect to the therapeutic effect of anti-angiogenesis agents, especially thalidomide itself, on the specific type of cancer, hepatocellular carcinoma. Based on these citations, persons with ordinary skill in the art can by no means be motivated to use or have a reasonable expectation of success that thalidomide alone can be used to treat hepatocellular carcinoma as claimed in the subject application. The cited references, either alone or in combination, do not render the current claims 9 and 11 obvious. The rejections under 35 USC 103 must be withdrawn.

Accordingly, applicants submit that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

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PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA

BACKGROUND OF THE INVENTION

Thalidomide was first synthesized in 1953, and it was widely used as a sedative and for the prevention of vomiting during pregnancy. In 1963, it was found that women who took thalidomide in the first trimester of pregnancy would deliver terata, such as phocomelia. Therefore, thalidomide was prohibited in Europe and the USA.

In view of studies in recent years, thalidomide has the efficacy on adjustment of the immune system which may treat immune system related diseases. For instance, Arch Dermatol. 1993, vol. 129, p. 1548-1550 described the use of thalidomide in the treatment of cutaneous lupus erythematosus; the Journal of Rheumatology, 1989, 16, p. 159-163 described the use of thalidomide in the treatment of refractory rheumatoid arthritis; Arch Dermatol. 1990, vol. 126, p. 923-927 described the use of thalidomide in the treatment of Behcet's syndrome; Journal of Pediatr. Gastroenerol. Nurt. 1999, vol. 28, p. 214-216 described the use of thalidomide in the treatment of Cornh's disease; and Journal of Rheumatology, 1998, vol. 25, p. 964-969 described the use of thalidomide in the treatment of rheumatoid arthritis. In addition, US Patent Nos. 5,593,990 and 5,629,327 disclose that thalidomide could effectively inhibit angiogenesis; US Patent No. 5,654,312 discloses the methods of treatment for inflammatory and autoimmune dermatoses. In addition, the Journal of Infectious Diseases, 1993, 168, p. 408-414 taught that thalidomide could effectively inhibit tumor necrotic factor-alpha (TNF-I). Anti-Cancer Drugs, 1996, 7, p. 339-343 demonstrated that thalidomide could effectively inhibit basic fibroblast growth factor-induced angiogenesis. Thalidomide is widely applied in the clinical treatment of malignant tumors which are highly vascular and cannot be effectively treated by chemical therapy. For instance, US Patent No. 5,696,092 discloses the use of thalidomide in the

inhibition of metastases of cancers of epithelial cell origin, especially human prostate cancers. Among the above prior art references, none of the references or patents teaches that thalidomide could be specifically used in the treatment of hepatocellular carcinoma.

Up to the present time, there are not any drugs that can effectively treat hepatocellular carcinoma. Patients with metastatic hepatocellular carcinoma or hepatocellular carcinoma, where local treatment has failed, normally survive for only three to four months. Metastatic hepatocellular carcinoma or hepatocellular carcinoma, where local treatment has failed, is mainly subjected to systemic therapy. The use of Doxorubicin, a high dosage of Tamoxifen in combination Doxorubicin or EA-PFL, is an effective example. The remission rate of those drugs can achieve levels between 15 and 30%. However, because the patients of hepatocellular carcinoma usually develop complication of liver cirrhosis and other complications (such as leukopenia, thrombopenia or liver function impairment), they cannot be subject to systemic chemotherapy.

DESCRIPTION OF THE DRAWINGS

Figure 1 shows a computerized abdominal tomography of a patient, before and after, treatment with thalidomide. Fig. 1(a) and Fig. 1(b): before the treatment with thalidomide, the computerized abdominal tomography scan shows that the left and right hepatic lobes of the patient were infiltrated with diffused hepatocellular carcinoma. The depositing of Lipiodol on the liver lobes after arterial embolization is shown in Fig. 1(a) and Fig. 1(b). Fig. 1(b) also shows a 5 cm × 5 cm massive type index lesion at the left hepatic lobes. The concentration of alpha-fetoprotein in the patient's blood is 4335 μg/ml. Fig. 1(c) and Fig. 1(d): after treatment with thalidomide, the computerized abdominal tomography scan shows that most diffused hepatocellular carcinoma, which infiltrated the left and right hepatic lobes of the patient, disappear. The massive type index lesion at the left hepatic lobe shown in Fig. 1(b) has been reduced to the size of 3 cm × 3 cm. The concentration of alpha-fetoprotein in the patient's blood is

1501 μg/ml. In addition, the scan show the occurrence of ascitic fluid. After the detection by abdominal paracentesis, it is proved that ascitic fluid was caused by spontaneous bacterial peritonitis. The existence of hepatocellular carcinoma was not shown.

Figure 2 shows the variation of the concentrations of alpha-fetoprotein in the patient's blood before and after the treatment with thalidomide.

SUMMARY OF THE INVENTION

An object of the subject invention is to provide a pharmaceutical composition for use in the treatment of hepatocellular carcinoma.

Another object of the subject invention is to provide a pharmaceutical composition for use in the treatment of metastatic hepatocellular carcinoma or hepatocellular carcinoma, where local treatment has failed, which comprises thalidomide and a pharmaceutically acceptable carrier.

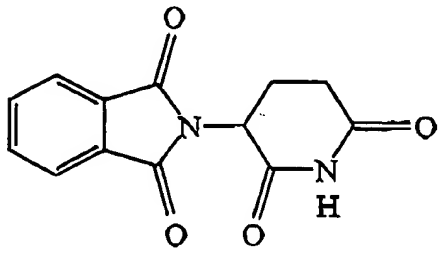
Another object of the subject invention is to provide a pharmaceutical composition used as adjuvant treatment for hepatocellular carcinoma, where local treatment has failed, such as percutaneous ethanol injection, operation, transcatheter arterial chemoembolization (TACE) or cryotherapy.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention utilizes thalidomide to treat metastatic hepatocellular carcinoma and hepatocellular carcinoma, where local treatment has failed. Occasionally, the invention found that thalidomide has excellent effects concerning the treatment of such carcinoma which are difficult to treat. This includes the significant and rapid decrease of the concentration of alpha-fetoprotein, the reduction of tumors and the relief of symptoms for patients, without significant side effects, such as arrest of

bone mellow or hepatotoxicity.

The chemical nomenclature of thalidomide used in the subject invention is 2-(2,6-dioxo-3-piperidinyl)-1H-isoindolle-1,3(2H)-dione, which is a white crystal powder; odorless; mp 269-271 □C; sparingly soluble in water, methanol, ethanol or acetone. The chemical structure of thalidomide is as follows:



The term "pharmaceutically effective amount" used in the pharmaceutical composition of the subject invention is directed to the administered amount to mammals that need such treatment in order to proceed with the above-mentioned treatment. The pharmaceutically effective amount depends on the individual, the disease to be treated, the body weight and age of the individual, the level of the disease or the administration route. This can be determined by persons skilled in the art. The pharmaceutically effective amount of thalidomide used in the subject invention is usually 30 to 1200 mg, preferably 50 to 800 mg and more preferably 100 to 500 mg.

The pharmaceutical composition of the subject invention can be used in combination with other hepatocellular carcinoma treating drugs, such as anticancer chemotherapeutic drugs, hormones, biological response modifier(s), other angiogenesis inhibitors, immunological inhibition agents or gene therapeutic agents.

The pharmaceutical composition of the subject invention can be administered by different routes, comprising oral, rectal, topical subcutaneous, intravenous, intramuscular and nasal administration. The

compound is effective in both injective composition or oral composition form.

The therapeutic efficacy of the pharmaceutical composition of the subject invention comprising thalidomide on the treatment of hepatocellular carcinoma has been supported by clinical observation.

An example is as follows:

A 44 year-old male patient with medical history of hepatitis C was diagnosed with hepatocellular carcinoma in December 1998 and treated with transcatheter arterial chemoembolization. He was treated with transcatheter arterial chemoembolization again in March and June 1999. According to the computerized abdominal tomography and gastrointestinal track barium enema, hepatocellular carcinoma invasion of the right colon and duodenum was doubted. The patient was treated with radiation on the right liver lobe during July to September 1999. After one-month of treatment, the concentration of alpha-fetoprotein in the patient's blood increased from 105μg/ml, before treatment, to 535 μg/ml. The follow-up magnetic resonance imaging (MRI) revealed that the hepatocellular carcinoma of the patient exacerbated and was complicated with tumor thrombosis of a portal vein. The patient was treated with a forth transcatheter arterial chemoembolization. The concentration of alpha-fetoprotein in the patient's blood was increased to 1572 μg/ml. In November 1999, the follow-up computerized abdominal tomography scan showed that the two hepatic lobes of the patient had wide hepatocellular carcinoma infiltration (as shown in Figs. 1(a) and 1(b)), esophageal and gastric varcose, tumor thrombosis of a portal vein and the main portal vain in the liver. The concentration of alpha-fetoprotein in the patient's blood was up to 4335 μg/ml. The liver function exacerbated that the total bilirubin was 9.2 mg%, GOT/GPT was 253/115 IU and alkaline phosphase (ALP) was 239 unit/l. As the liver function of the patient was significantly exacerbated, he was not suitable to take transcatheter arterial embolization therapy. 100 mg of Thalidomide was administered to the patient twice per

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*** ACTIVITY REPORT ***
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ST. TIME	DESTINATION TEL/ID	NO.	MODE		PGS.	RESULT
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10/20 07:13	0115114411916	0108	TRANSMIT	ECM	1	OK 00'21

day. After two weeks of treatment, upper quadrant tenderness of the patient was significantly relieved. After four weeks, the concentration of alpha-fetoprotein in the patient's blood was decreased to 1501 μg/ml, total bilirubin was 10.2 mg%, GOT/GPT was 184/102 IU and alkaline phosphase was 233 unit/l. Meanwhile, the follow-up MRI showed that the hepatocellular carcinoma of the two liver lobes significantly remitted (as shown on left lower and right lower figures). However, ascitic fluid was found. The abdominal paracentesis evidenced that ascitic fluid was caused by spontaneous bacterial peritonitis. The existence of hepatocellular carcinoma was not shown. The patient was administered with antibiotics for the treatment of spontaneous bacterial peritonitis. The patient was still treated with thalidomide to the present. Figure 2 shows the variation in the concentrations of alpha-fetoprotein in the patient's blood. After treatment with thalidomide, the concentration of alpha-fetoprotein significantly decreases.

Claims:

1. A pharmaceutical composition for use in the treatment of hepatocellular carcinoma, comprising a pharmaceutically effective amount of thalidomide and a pharmaceutical acceptable carrier.

2. The pharmaceutical composition according to Claim 1, wherein the pharmaceutically effective amount is 30 to 1200 mg.

3. The pharmaceutical composition according to Claim 2, wherein the pharmaceutically effective amount is 50 to 800 mg.

4. The pharmaceutical composition according to Claim 1 for use in the treatment of metastatic hepatocellular carcinoma, where local treatment has failed.

5. The pharmaceutical composition according to Claim 1, which is used in combination with an additional drug for treating hepatocellular carcinoma, selected from a group consisting of anticancer chemotherapeutic drugs, hormones, biological response modifiers or other angiogenesis inhibitors; or in combination with immunotherapy or gene therapy.

6. The pharmaceutical composition according to Claim 1 for use as an adjuvant treating agent in the treatment of hepatocellular carcinoma.

7. The pharmaceutical composition according to Claim 6, wherein the treatment of hepatocellular carcinoma is a percutaneous ethanol injection, operation, transcatheter arterial chemoembolization or cryotherapy.

ABSTRACT OF THE INVENTION

The invention mainly discloses a pharmaceutical composition for use in the treatment of hepatocellular carcinoma, which comprises thalidomide and a pharmaceutically acceptable carrier.

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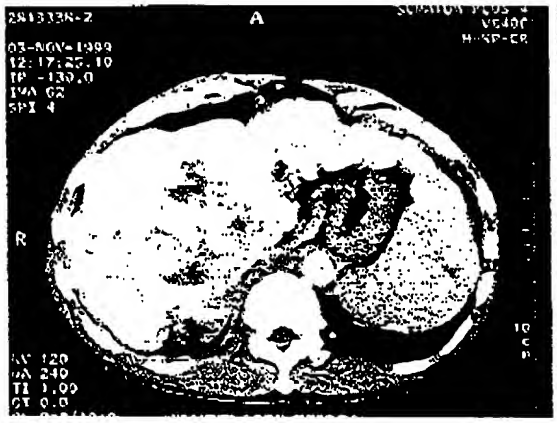

FIG.1a

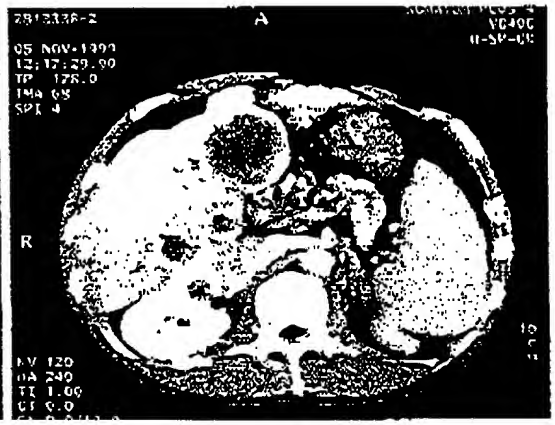

FIG.1b

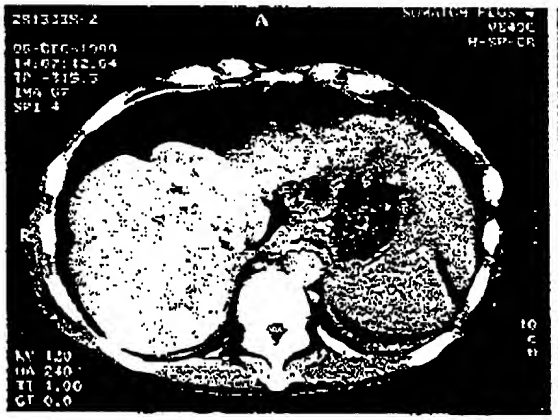

FIG.1c

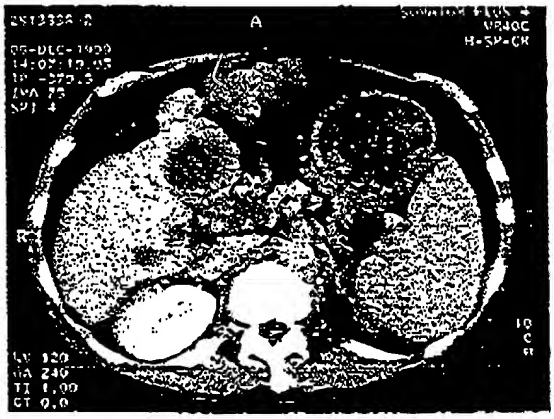

FIG.1d

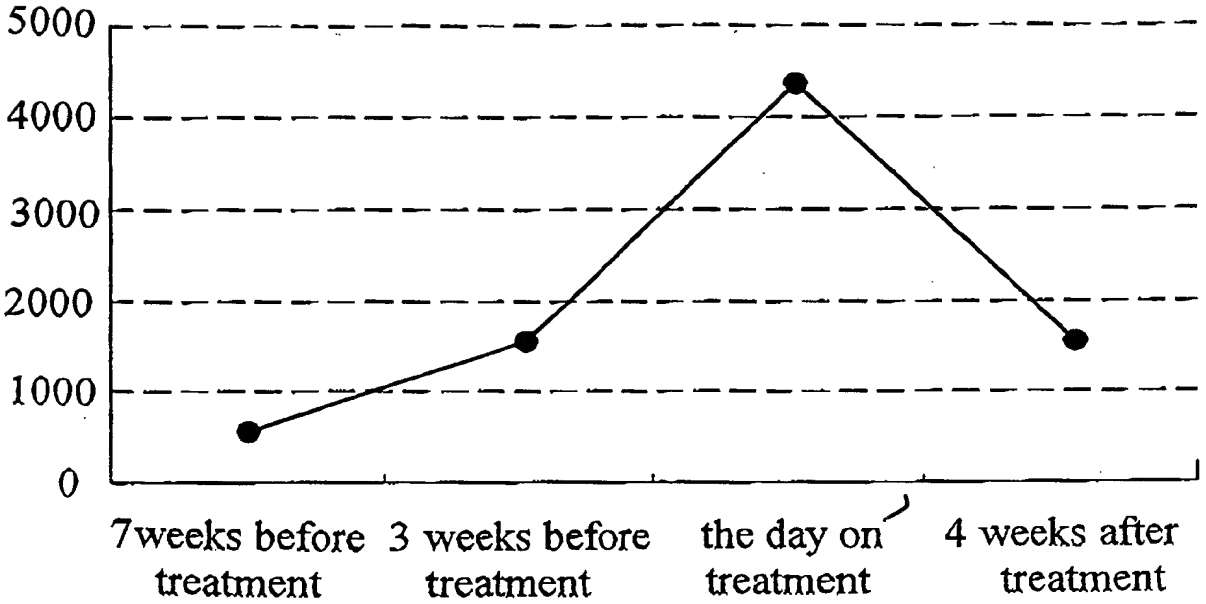
5000
4000
3000
2000
1000
0
7weeks before treatment
3 weeks before treatment
the day on treatment
4 weeks after treatment

FIG.2

Enclosure 2

LIPPINCOTT WILLIAMS & WILKINS

American Journal of Clinical Oncology & Cancer Clinical Trials

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Am J Clin Oncol (CCT) 23(3): 319–321, 2000.

Clinical Case Reports
FROM M.D. ANDERSON CANCER CENTER

Aman U. Buzdar, Editor; Christine F. Wogan, Assistant Editor

Durable Clinical Response of Refractory Hepatocellular Carcinoma to Orally Administered Thalidomide

Yehuda Z. Patt, M.D., Manal M. Hassan, M.D., Ph.D., Richard D. Lozano, R.Ph., Lee M. Ellis, M.D., J. Andrew Peterson, M.D., and Kimberly A. Waugh, M.D.

Thalidomide, a sedative agent previously associated with severe fetal malformations, has anti-angiogenic activity. We describe the antitumor effects of thalidomide in a patient with hepatocellular carcinoma that was refractory to systemic and intraarterial therapy.

Key Words: Hepatocellular carcinoma—Thalidomide—Angiogenesis.

Drs. Yehuda Z. Patt, Manal M. Hassan, Lee M. Ellis, Kimberly A. Waugh, and Richard D. Lozano

Angiogenesis, a highly regulated process that leads to the formation of new blood vessels, has been described as essential for solid tumor growth.[1,2] Tumor angiogenesis is thought to be induced by a shift in the balance typically maintained between angiogenic inducers and angiogenic inhibitors.[3] These observations have led to the concept that angiogenesis inhibitors could be used to treat neoplasms, especially vascularized ones. Thalidomide, a sedative agent previously associated with severe fetal malformations, has been studied for its anti-angiogenic activity. We describe the antitumor effects of thalidomide in a patient with hepatocellular carcinoma (HCC) that was refractory to systemic[4–7] and intraarterial therapy.[8,9]

From the Departments of Gastrointestinal Medical Oncology and Digestive Diseases (Y.Z.P., M.M.H.), Pharmacy (R.D.L.), Surgical Oncology (L.M.E.), and Diagnostic Radiology (K.A.W.), The University of Texas M. D. Anderson Cancer Center, Houston, Texas, and 1201 5th Avenue North, Suite 505, St. Petersburg, Florida (J.A.P.).

Address correspondence and reprints requests to Christine F. Wogan, Department of Scientific Publications, Box 234, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, U.S.A.

CASE HISTORY

Dr. J. Andrew Peterson

A 67-year-old white man was admitted to a local hospital in St. Petersburg, Florida, for a single episode of abdominal pain. Computed tomography (CT) scans of the abdomen on April 17, 1997, showed a large (6-cm), well-demarcated mass in the medial segment of the left hepatic lobe and two other lesions in the right hepatic lobe. Upper and lower gastrointestinal endoscopy failed to show any primary gastrointestinal malignancy. Fine needle aspiration of the tumor confirmed a diagnosis of HCC, and about two weeks later the patient was referred to The University of Texas M. D. Anderson Cancer Center.

Drs. Yehuda Z. Patt, Lee M. Ellis, Richard D. Lozano, and Kimberly A. Waugh

At M. D. Anderson, the histologic diagnosis of HCC was confirmed, and the laboratory findings were as

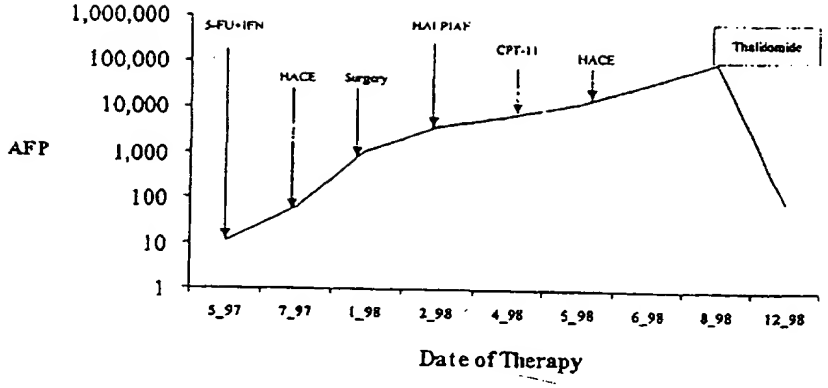

FIG. 1. Alpha-fetoprotein levels (AFP; in ng/dl) during treatment of a 67-year-old man with alcoholic cirrhosis and hepatocellular carcinoma. 5-FU+IFN, 5-fluorouracil and recombinant interferon alfa-2b; HACE, hepatic arterial chemoembolization; HAI PIAF, hepatic arterial infusion of cisplatin, IFN, doxorubicin, and 5-FU; CPT-11, irinotecan.

follows: hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C virus antibody were all nonreactive; serum bilirubin was 1.3 mg/dl; alpha-fetoprotein (AFP) was 8.7 ng/ml; serum albumin was 3.6 g/dl; hemoglobin was 12.1 g/dl; the white blood cell count was 11,600/μl; and the platelet count was 439,000/μl. Electrolyte levels were normal. Initial therapy included continuous intravenous infusion of 5-fluorouracil (5-FU) and recombinant interferon alfa-2b (rIFNα2b). An evaluation on July 8, 1997, showed no change in the size of the liver tumor, but the AFP level had increased to 60.5 ng/ml (Fig. 1). Two weeks later, the patient underwent a single chemoembolization of the left hepatic artery with cisplatin, doxorubicin (Adriamycin), and mitomycin C. Chemoembolization was not repeated because of the patient's business commitments.

In January 1998, the patient underwent exploratory surgery to determine whether the tumor could be resected. Adequate resection margins would have required a left hepatic lobectomy, which was likely to have only palliative benefits; moreover, the patient's alcoholic cirrhosis made him a poor candidate for that procedure. Subsequent treatment initiated in February 1998 included percutaneous hepatic arterial infusion with cisplatin, rIFNα2b, doxorubicin, and 5-FU.[8] However, the tumor continued to grow, and the serum AFP level continued to increase (Fig. 1). Neither systemic irinotecan (CPT-11) nor repeat chemoembolization of the left hepatic artery with mitomycin C, doxorubicin, and cisplatin produced an antitumor response, and the patient's serum AFP level continued to climb, peaking at 109,118 ng/ml (Fig. 1). The patient's general condition deteriorated; symptoms included evidence of partial obstruction of the gastric outlet, an increase in serum bilirubin to 1.8 mg/dl, and a decrease in serum albumin to 3.3 g/dl.

In August 1998, therapy with oral thalidomide was begun at 400 mg/d; the dose was increased to 800 mg/d in week 2 and to 1,200 mg/d from week 3 onward. The main side effect of thalidomide was sedation. The patient's performance status improved substantially. Specifically, evidence of gastric outlet obstruction disappeared, serum AFP decreased to 99.1 ng/ml by December 1998 (Fig. 1), and CT scans in January 1999 showed dramatic shrinkage of both the left lobe HCC and the right lobe metastases (Fig. 2). As of July 1999, the patient was continuing to take thalidomide at a dose of 600 mg/d; the only reported side effects is drowsiness, which is relieved by methylphenidate hydrochloride (Ritalin).

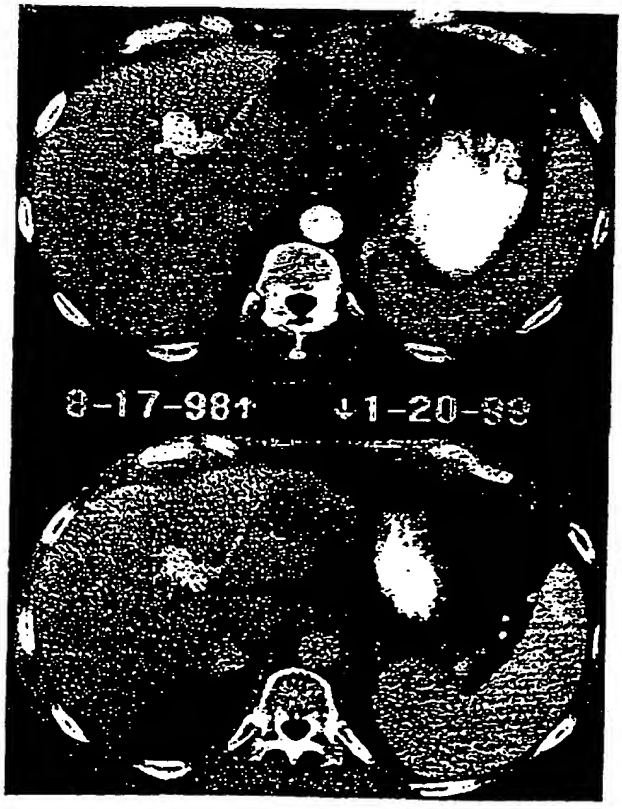

FIG. 2. Computed tomography scans of the abdomen before (top) and after (bottom) 5 months of treatment with thalidomide. The bottom scan shows shrinkage of the tumors in the left and right lobes of the liver.

DISCUSSION

Drs. Yehuda Z. Patt, Lee M. Ellis, Kimberly A. Waugh, and Manal M. Hassan

About 60% of all HCCs develop in patients with severe cirrhosis who are poor candidates for more aggressive chemotherapy. Moreover, the prognosis for patients with metastatic refractory HCC is usually poor. This patient's HCC responded well to oral thalidomide, the antitumor activity of which is presumably related to its anti-angiogenic activity.

The anti-angiogenic activity of thalidomide, a sedative and anti-inflammatory agent, was first demonstrated in a rabbit cornea micropocket assay.[10] In that study, orally administered thalidomide was found to inhibit angiogenesis that had been induced by basic fibroblast growth factor. The mechanism by which thalidomide inhibits angiogenesis in cancer, however, is not entirely clear. In one study, thalidomide was found to modulate the activity of tumor necrosis factor-alpha in human monocytes by accelerating the degradation of its mRNA.[11] More recent evidence suggests that thalidomide's anti-angiogenic effect requires metabolic activation and is probably species-specific.[12] A recent study of the angiogenesis inhibitor TNP-470 showed that this agent inhibited both the growth of primary tumors and the formation of liver metastases from gastric and colon cancer xenografts in nude mice.[13] In addition, in a rat hepatoma model, TNP-470 enhanced apoptosis in hepatic metastases and improved survival.[13] The author of this study hypothesized that angiogenesis inhibitors may maintain micrometastases in a dormant state and that those dormant micrometastases could be treated with cytotoxic drugs.

Because thalidomide seems to be well tolerated except for some drowsiness, it may be suitable for long-term maintenance therapy after tumors have been reduced to the dormant state.[14] However, thalidomide may not be appropriate for all patients because of its teratogenicity. We recommend that all sexually active women considering treatment with thalidomide be given a pregnancy test no earlier than the day before such treatment is to begin and that they use at least two methods of contraception (e.g., hormonal plus barrier) during the treatment. A formal phase II trial has been initiated at M. D. Anderson to investigate the antitumor activity of thalidomide in HCC.

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In re application of: CHUN-YIN HUANG

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